

An Overview of Influenza Viruses and Novel H1N1

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Q1: The age group with the highest attack rate of novel H1N1 (swine flu) is

- A) 0 to 4 years
- B) 5-14 years
- C) 15-24 years
- D) 25-64 years
- E) 65 years and over

Q2: The highest priority group for nH1N1 vaccine of the following is:

- A) Young adults aged 25-35
- B) Police and fire personnel of any age
- C) Pregnant women of any age
- D) Persons who do not receive the 2009 seasonal influenza vaccine



An emergency hospital at Camp Funston, Kansas, cared for large numbers of soldiers sickened by the 1918 flu. (Credit: The National Museum of Health and Medicine, Armed Forces Institute of Pathology, Washington, D.C. Image number NCP 1603).

Importance of 1918 Strain

- "The 1918-1919 influenza pandemic was a defining event in the history of public health. The legacy of that pandemic lives on in many ways, including the fact that the descendants of the 1918 virus have continued to circulate for 9 decades."

--Dr. Anthony S. Fauci, NIAID Director

Some Flu Epidemics of 20th Century

| Date | Strain | Subtype |
|----------------------|--------|------------------------------------|
| 1918 | H1N1 | pandemic of <u>"Spanish" flu</u> |
| 1957 A/Singapore/57 | H2N2 | pandemic of "Asian" flu |
| 1962 A/Japan/62 | H2N2 | epidemic |
| 1964 A/Taiwan/64 | H2N2 | epidemic |
| 1968 A/Aichi/68 | H3N2 | pandemic of "Hong Kong" flu |
| 1976 A/New Jersey/76 | H1N1 | Non-epidemic swine flu in recruits |
| 1977 A/USSR/90/77 | H1N1 | "Russian" flu |

Timeline of Emergence *Influenza A Viruses in Humans*



Influenza

3 major types: A, B, C

- A causes pandemics
- B may cause outbreaks
- C rarely causes human disease

Further Classification

- Type A has subtypes—specific H, N:
eg influenza A "H2N2"
- Strain—specific site and year of
isolation: "A/Victoria/75 (H3N2)"

2009-10 Novel H1N1 Vaccine

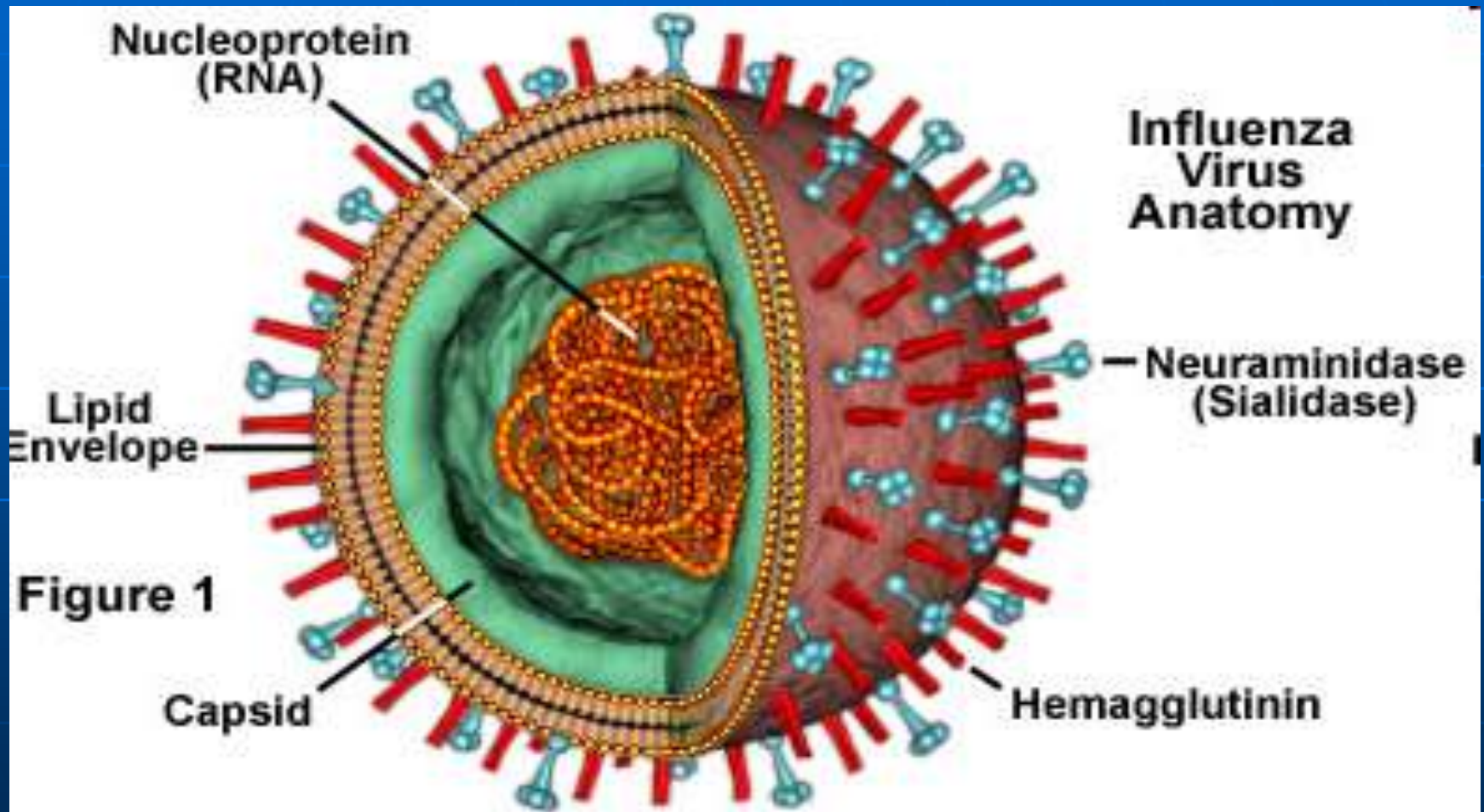
- A/California/7/2009 (H1N1)v

Influenza A Virus

An enveloped virus, enclosed in a **lipid bilayer** (from the plasma membrane of its host)

- Within the lipid bilayer are two integral membrane proteins
 - **hemagglutinin ("H")** and
 - **neuraminidase ("N")**
- Inside the lipid bilayer are
 - some 3000 molecules of **matrix protein**
 - **8 pieces of RNA, each one a gene**
 - **RNA polymerase**

Structure of the Influenza Virus



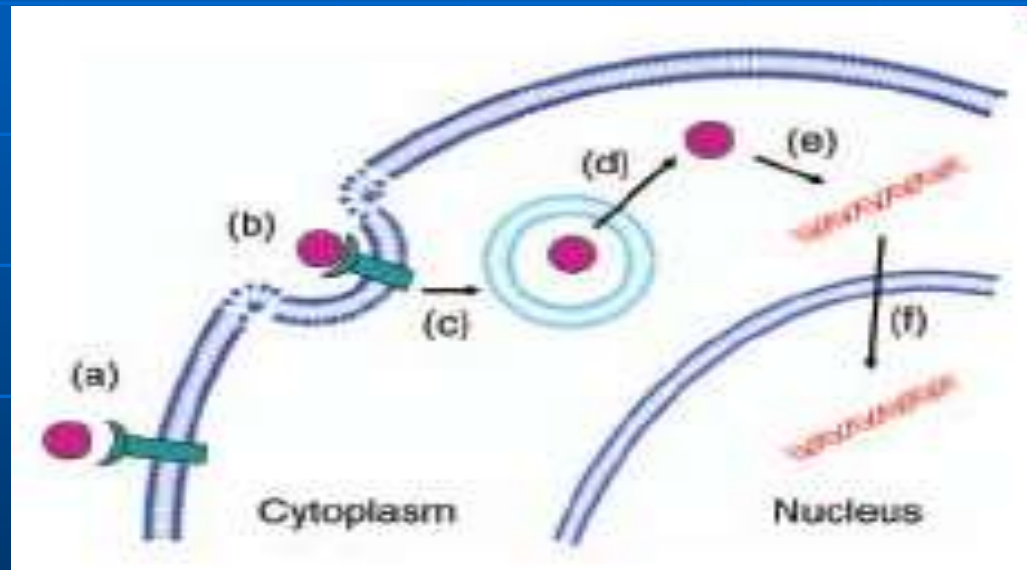
Genes of the Influenza Virus

- Flu viruses have 8 genes:
- Hemagglutinin (H) and neuraminidase (N) genes code for proteins on the virus surface that allow the virus to enter and exit the cell.
- 16 H subtypes and 9 N subtypes, making 144 possible H-N combinations. Subtle variations in these 2 proteins affect recognition by the immune system

How Does the Flu Virus Gain Access to the Body?

- The influenza virus contacts cells of the respiratory tract.
- HA (H) molecules bind to surface of the cells of the host respiratory system.
- The virus is engulfed by endocytosis, forming a vesicle.
- The viral H fuses with the vesicle membrane and enters the cell
- Viral RNA enter the nucleus of the cell, reproduces.
- RNA exits nucleus, is translated into viral proteins
- New virus buds off from the plasma membrane of the cell, using NA
- The cycle repeats

Viral Entry Into Cell

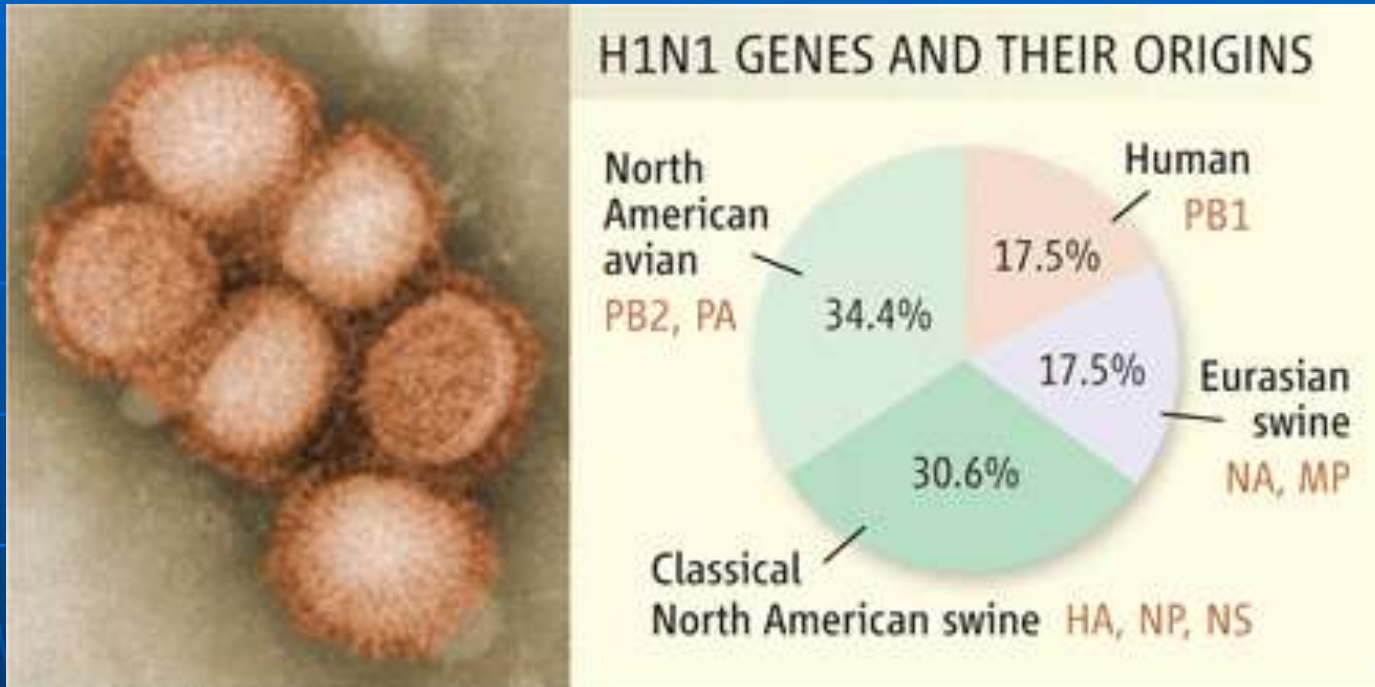


First Recognition

- In spring 2009 a new influenza, or flu, virus began causing illness in Mexico. Unofficially called "swine flu" it is now officially referred to as "novel H1N1."

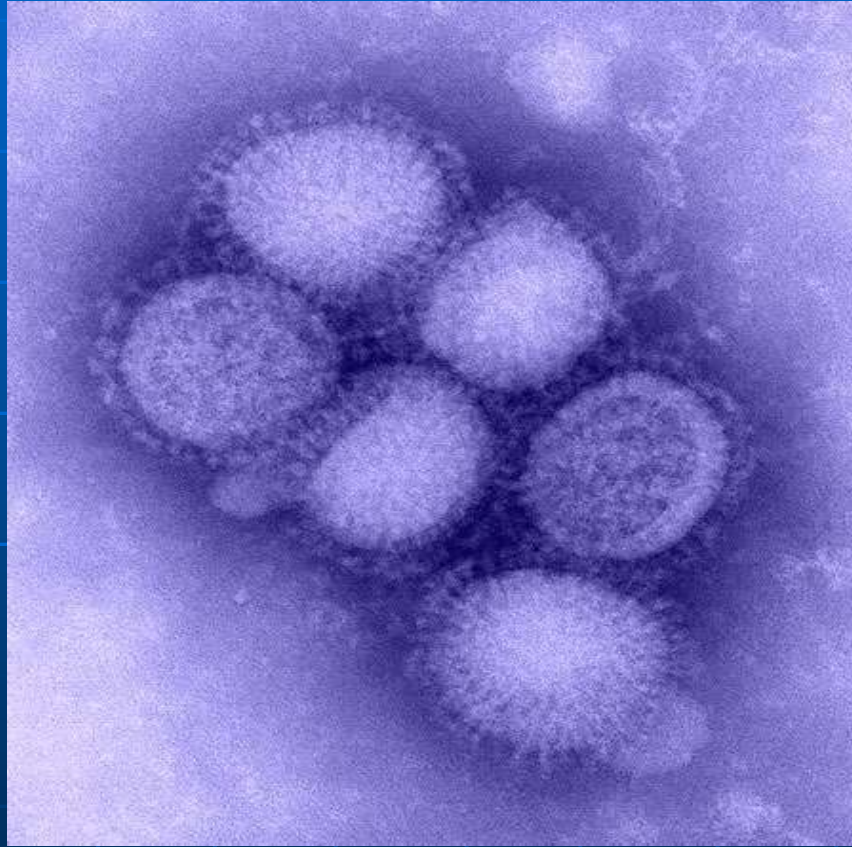
Origin

- Novel H1N1 virus is related not only to swine viruses but also of the H1N1 virus that caused the 1918 pandemic, which killed 40-50 million people worldwide.



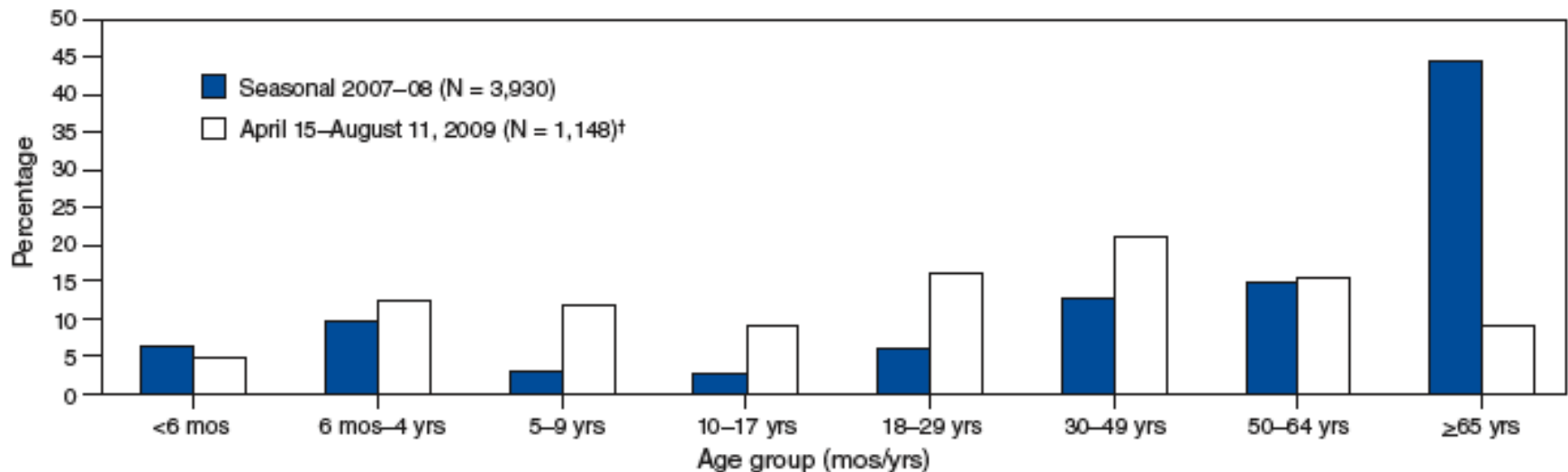
J. Cohen Science 324, 700 -702 (2009)

H1N1 Virus



Hospitalization: Age Group Distribution

FIGURE. Distribution by age group of persons hospitalized with laboratory-confirmed influenza,* — United States, 2007–08 winter influenza season and April 15–August 11, 2009



Source: Emerging Infections Program, CDC.

* Evidence of a positive influenza test result by viral culture, direct fluorescent assay, immunofluorescence assay, real-time reverse-transcription polymerase chain reaction, rapid influenza diagnostic test, serology, or written note in the medical chart.

† Influenza subtype cannot be determined with some types of tests, and the proportion of positive influenza tests that were attributable to novel influenza A (H1N1) virus cannot be determined. However, national surveillance for influenza viruses indicates that >95% of viruses circulating during this time were novel influenza A (H1N1) virus.

Differences in Clinical Effects of H1N1

- Younger persons represent higher percentage of cases
- Higher rate of complications among obese persons?
- Lower prevalence of fever?
- Higher prevalence of GI symptoms?

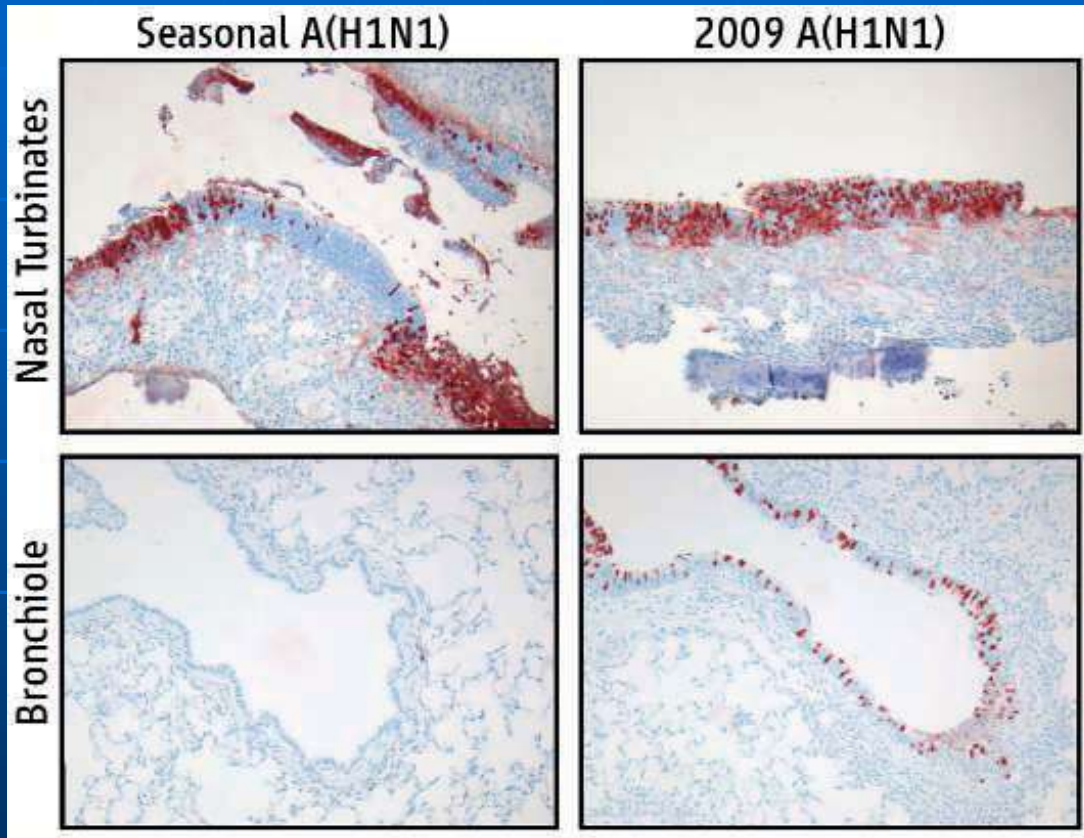
Science, July 2009

- Research groups from MIT and CDC recently collaborated to test the ability of novel H1N1 to spread and cause disease. They isolated viruses from 3 patients and infected mice and ferrets. The results were published online ahead of print on July 2, 2009, in *Science*.

Science, July 2009

- Findings: compared to seasonal H1N1 flu viruses, novel H1N1 viruses replicated to higher levels in lung tissue .
- Virus also found in GI tracts of the ferrets, which might explain reports of gastrointestinal problems in some infected people.
- Novel H1N1 viruses transmitted less efficiently between ferrets in respiratory droplets than seasonal H1N1.

Viral Binding to Respiratory Tract



CREDIT: VINCENT J. MUNSTER *ET AL.*, *SCIENCE*, July 2, 2009

RESISTANCE OF PANDEMIC INFLUENZA H1N1v VIRUSES TO ADAMANTANES (M2 BLOCKERS): Amantadine & Rimantadine

| | Isolates Tested Tested (n) | | Resistant Isolates | % Resistant |
|---------------------------|-------------------------------|------------|-----------------------|----------------|
| ■ US Isolates | 305 | 305 | | 100 |
| ■ Foreign Isolates | 78 | 78 | | 100 |
| ■ Global Isolates | 383 | 383 | | 100 |

Alexander Klimov, PhD Influenza Division National Center for Immunizations and Respiratory
Diseases Centers for Disease Control and Prevention

RESISTANCE OF PANDEMIC INFLUENZA H1N1v VIRUSES TO NEURAMINIDASE INHIBITORS:

Oseltamivir (Tamiflu) and Zanamivir (Relenza)

(Block the viral N and thus inhibit release of virus)

| | Isolates Tested | Resistant (%) |
|---|-----------------|---------------|
| ■ US isolates | 267 | 0 (0) |
| ■ | | |
| ■ Foreign isolates | 105 | 0 (0) |
| ■ | | |
| ■ Global isolates | 372 | 0 (0) |
| ■ | | |
| ■ Seven oseltamivir-resistant cases were recently documented: | | |
| ■ Denmark (after oseltamivir treatment) | | |
| ■ Japan (4) (after oseltamivir treatment) | | |
| ■ Canada (after oseltamivir treatment) | | |
| ■ Hong Kong (travel from U.S., no treatment) | | |

Any Cross-Protection from Seasonal Vaccine?

- Vaccination with recent seasonal trivalent influenza vaccines (TIV), resulted in a >4-fold rises in cross-reactive antibody to the pandemic virus in:
 - only about 2% of children aged 6 months to 9 yrs,
 - 12-22% of adults 18-64 years, and
 - <5% of adults aged >60 years.

CDC

Mutations in H1N1?

- H1N1 strains show only minor genetic variability
- No evidence of re-assortment with seasonal or H5N1 viruses

CDC

Distribution of cases/hospitalizations/deaths

- –Highest incidence lab confirmed infections (150/100,000) in children 5-14 yrs old
- –Highest hospitalization rates among 0-4 year olds (25/100,000), then 5-14 yr olds (11/100,000)
- –Hospitalization rates for Apr-Jul 2009 approach cumulative rates for seasonal influenza among school age children and 19 through 49 year old adults
- –Fewest cases but highest case-fatality ratio in older adults

Cross-Reacting Ab

- Cross-reactive antibody to nH1 was detected among adults participants in vaccine studies
 - –6%--9% of those aged 18--64 years
 - –33% of those aged >60 years
 - –0% of children
- Await clinical studies to see whether older adults with some pre-existing immunity might need only a single dose

CDC

Groups Affected

- Distribution of cases by age group is markedly different compared to seasonal influenza
 - –Young children have highest attack rate
 - –Far fewer cases in older adults
- –No outbreaks among elderly in long term care facilities
- 70% of hospitalized cases have an underlying medical condition that confers higher risk for complications
- Pregnancy is a higher risk condition

CDC

August 28 CDC Update

- Proportion of pneumonia+influenza deaths was in normal range for summer 2009
- Virtually all Aug 2009 viruses are nH1N1
- No major mutations of nH1N1 since vaccine strain chosen
- Oseltamivir/zanamivir susceptibility remains, with rare exceptions

CDC

8/28 Update

- Experience in Southern Hemisphere very similar to US experience in Spring 2009
- Decreases in disease activity in South America, Australia, UK

CDC

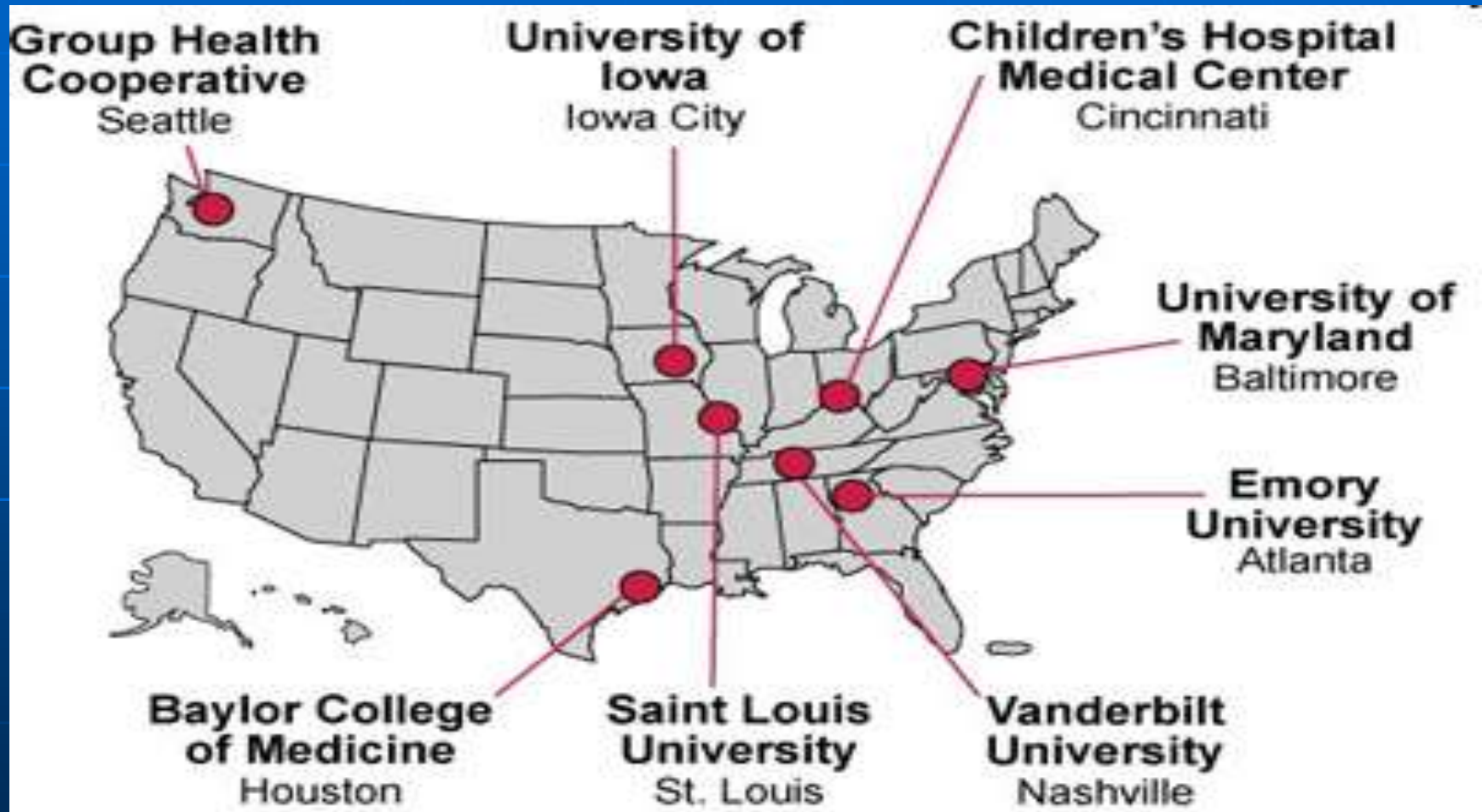
Testing for H1N1 r-RT-PCR



The Vaccine



NIH Vaccine Treatment and Evaluation Units (VTEUs)



Goals of Vaccine Trials

- One vs two 15 mcg doses
- One vs two 30 mcg doses
 - Doses 3 wks apart. Adults in trials first, then children 6 mo to 17 yrs
- Is seasonal flu vaccine safe and effective if given with H1N1 vaccine?
- Ability to enroll large number (thousands) of volunteers *rapidly*

Initial Target Groups

ACIP has designated 5 target groups (order of target groups does not indicate priority):

- pregnant women,
- persons who live with or provide care for infants aged <6 months (e.g., parents, siblings, and daycare providers),
- health-care and emergency medical services personnel,
- persons aged 6 months--24 years, and
- persons aged 25--64 years who have medical conditions that put them at higher risk for influenza-related complications.

Subset of Target Groups During Limited Vaccine Availability

If the supply of the vaccine initially available is not adequate to meet demand, ACIP recommends that the following subset of the initial target groups receive priority (order of target groups does not indicate priority):

- pregnant women,
- persons who live with or provide care for infants aged <6 months (e.g., parents, siblings, and daycare providers),
- health-care and emergency medical services personnel who have direct contact with patients or infectious material,
- children aged 6 months--4 years, and
- children and adolescents aged 5--18 years who have medical conditions that put them at higher risk for influenza-related complications.

Medications

- **Amantadine and Rimantadine**
 - Appear of no value vs H1N1, due to viral resistance
- **Oseltamavir (Tamiflu) and zanamavir (Relenza)**
 - Seasonal flu strains resistant, but H1N1 is sensitive.
- **Antibiotics** are of absolutely no value against the influenza

Preparing for H1N1

- Public health measures will be even more important before arrival of the H1N1 vaccine

Season Flu Concerns

- Seasonal flu vaccination still important and will proceed earlier this year
- Target groups for seasonal vaccine are same as in prior years and distinct from target for nH1N1
- Seasonal flu vaccine: H1N1(not pandemic strain), H3N2, B

Many Questions Remain

- Will oseltamivir (Tamiflu) be effective in late Fall or Winter 2009?
- What about zanamivir (Relenza)?



- Whom should we test for nH1N1 and treat with antivirals?
- In what setting will target groups be immunized against H1N1?

- • <4% of those born after 1979 had preexisting, cross-reactive, neutralizing antibody titers of ≥ 40 to H1N1v, whereas 34% of individuals born before 1950 had titers of ≥ 80

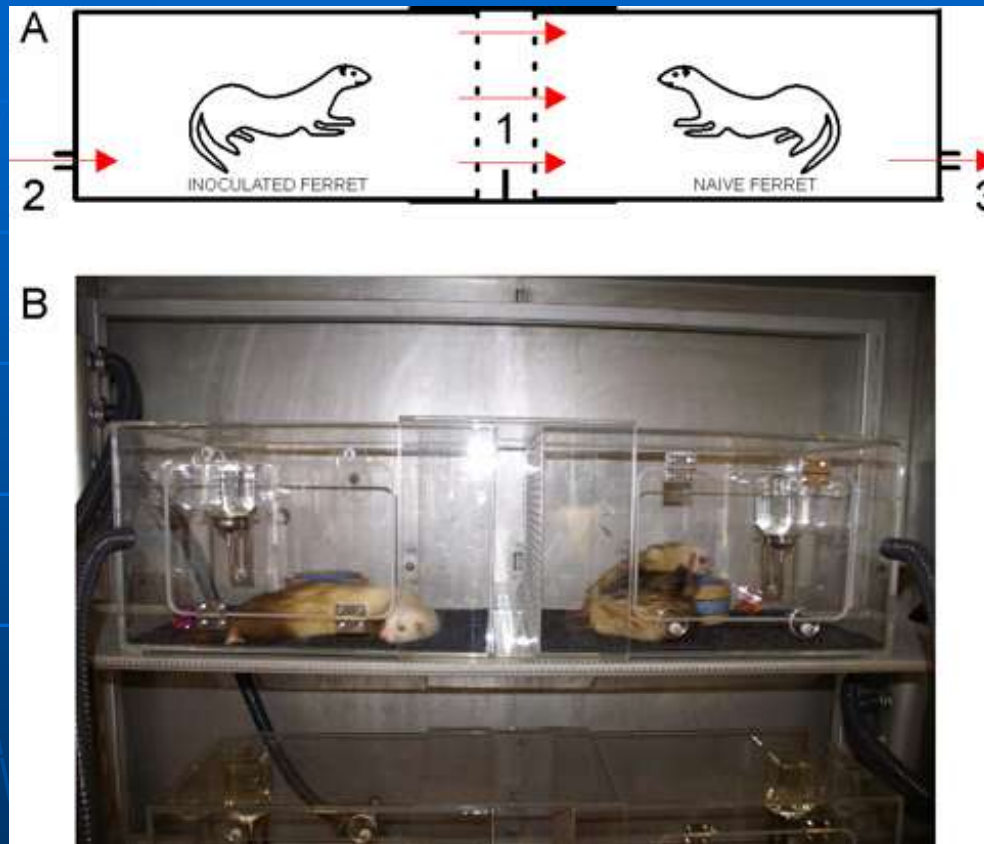
CDC

- Persons <30 years of age are serologically “naïve”–
- Some older adults appear to have pre-existing, cross-reactive antibodies

CDC

- Summary of key findings from virologic and immunologic studies
- •No significant antigenic changes among novel influenza A(H1N1) viruses since April 2009
- •Hemagglutinin of novel influenza A(H1N1) viruses is somewhat similar to H1 subtype viruses that circulated during 1920's-1940's

Transmission Studies



H1N1 Virus



Science, July 2009

- Novel H1N1 doesn't have a version of another gene called PB2 that has been associated with highly efficient virus transmission